Summary of Changes
BMT CTN 1301 PROGRESS II Amendment Version 4.0
Dated: June 22, 2017

The following changes, and the rationale for the changes, were made from Version 3.0 to Version 4.0 of the protocol. Additionally, there were a number of administrative changes, including corrections to typos and formatting.

#	Section number, title, and page number of original	Original text:	Changed to:	Rationale
1.	Protocol Synopsis – Eligibility Criteria Page ii	Patients ≥ 1 year and ≤ 65 years undergoing HSCT for treatment of acute leukemia in morphologic complete remission or myelodysplasia with < 5% blasts in the marrow and no circulating blasts, and who are eligible for a myeloablative allogeneic transplant. Patients with CMML must have a WBC count ≤ 10,000 cells/μL and < 5% blasts in the marrow.	Patients ≥ 1 year and < 66 years undergoing HSCT for treatment of acute leukemia in morphologic complete remission with or without hematologic recovery or myelodysplasia with < 5% blasts in the marrow and no circulating blasts, and who are eligible for a myeloablative allogeneic transplant. Patients with CMML must have a WBC count ≤ 10,000 cells/μL and < 5% blasts in the marrow. Patients with ≥ 5% blasts due to a regenerating marrow must contact the protocol chairs for review.	Corrected inconsistency in upper age limit; clarified leukemia eligibility criteria and added regenerating marrow language
2.	Protocol Synopsis –	Secondary objectives are: comparison of rates of grade II-IV and III-IV acute	Secondary objectives are: comparison of rates of grade II-IV and III-IV acute	Addition of “graft failure” as

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	Secondary Objectives Page ii	GVHD, chronic GVHD, chronic GVHD-free survival, immunosuppression-free survival at one year, neutrophil and platelet engraftment, disease relapse, transplant-related mortality, rates of Grade ≥ 3 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0; incidence of CMV and EBV reactivation, incidence of infections; immune reconstitution, quality of life and overall survival.	GVHD, chronic GVHD, chronic GVHD-free survival, immunosuppression-free survival at one year, primary and secondary graft failure, neutrophil and platelet engraftment, disease relapse, transplant-related mortality, rates of Grade ≥ 3 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0; incidence of CMV and EBV reactivation, incidence of infections; immune reconstitution, quality of life and overall survival.	secondary endpoint
3.	Study Schema Inclusion Criteria Page iv	2. Patients with acute leukemia, in morphologic complete remission or myelodysplasia with <5% blasts in the marrow and no circulating blasts. CMML must have a WBC count ≤ 10,000 cells/μL and < 5% blasts in the marrow.	2. Patients with acute leukemia, in morphologic complete remission with or without hematologic recovery or myelodysplasia with <5% blasts in the marrow and no circulating blasts. CMML must have a WBC count ≤ 10,000 cells/μL and < 5% blasts in the marrow. Patients with ≥ 5% blasts due to a regenerating marrow must contact the protocol chairs for review.	Clarification of leukemia eligibility criteria and addition of regenerating marrow language

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4.	Study Schema Exclusion Criteria Page iv	15. Planned post-transplant maintenance therapy except for FLT3 inhibitors or TKIs 16. *German centers only*: Treatment with any known non-marketed drug ...	15. Planned post-transplant maintenance therapy except for FLT3 inhibitors or TKIs a. Must be declared prior to randomization 16. Planned use of cryopreserved hematopoietic stem cells 17. *German centers only*: Treatment with any known non-marketed drug ...	Clarification of use of post maintenance therapy and new exclusion of cryopreserved cells
5.	Study Schema Secondary Endpoints Page v	**Secondary endpoints:** - Grades II-IV and III-IV acute GVHD - Chronic GVHD - Chronic GVHD-free survival - Immunosuppression-free survival at 1 year - Hematologic recovery - Immune reconstitution - Disease relapse - Transplant-related mortality - Toxicity (SOS and IPS) and rates of infections (CMV and EBV reactivation) - Relapse-Free and overall survival - Quality of life	**Secondary endpoints:** - Grades II-IV and III-IV acute GVHD - Chronic GVHD - Chronic GVHD-free survival - Immunosuppression-free survival at 1 year - Hematologic recovery - Primary and secondary graft failure - Immune reconstitution - Disease relapse - Transplant-related mortality - Toxicity (SOS and IPS) and rates of infections (CMV and EBV reactivation) - Relapse-Free and overall survival - Quality of life	Addition of new secondary endpoint “graft failure”
6.	Section 1.2. CD34+ Selection	*Not present in previous version.*	The CliniMACS® CD34 Reagent System was approved as a humanitarian	New information from Miltenyi

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	and T-Cell Depletion Page 1-2		device and authorized by U.S. Federal law for use in the treatment of patients with acute myeloid leukemia (AML) in first complete remission. The effectiveness of the device for this use has not been demonstrated.	CD34 Reagent IB, Version 8.0
7.	Section 2.3.1. Inclusion Criteria Page 2-1	2. Patients with acute leukemia in morphologic complete remission or with myelodysplasia (MDS) with no circulating blasts and with less than 5% blasts in the bone marrow. Patients with CMML must have a WBC count ≤ 10,000 cells/μL and < 5% blasts in the marrow.	2. Patients with acute leukemia in morphologic complete remission with or without hematologic recovery or with myelodysplasia (MDS) with no circulating blasts and with less than 5% blasts in the bone marrow. Patients with CMML must have a WBC count ≤ 10,000 cells/μL and < 5% blasts in the marrow. Patients with ≥ 5% blasts due to a regenerating marrow must contact the protocol chairs for review.	Clarification of leukemia eligibility criteria and addition of regenerating marrow language
8.	Section 2.3.2. Exclusion Criteria Page 2-3	15. Planned post-transplant maintenance therapy except for FLT3 inhibitors or TKIs 16. German centers only: Treatment with any known…	15. Planned post-transplant maintenance therapy except for FLT3 inhibitors or TKIs a. Must be declared prior to randomization 16. If it is known prior to enrollment that the hematopoietic stem cell product will	Clarification of use of post maintenance therapy and new exclusion of cryopreserved cells

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			need to be cryopreserved, **the patient should not be enrolled** 17. *German centers only*: Treatment with any known non-marketed drug ...	
9.	Section 2.4. Conditioning Regimens Page 2-4	Minor modifications to the myeloablative regimens that involve start day or days of rest in the Control Arm are allowed but must be approved by the protocol chairs. Only minor modifications will be considered for approval. Modifications to the myeloablative regimens in the intervention arms (CD34 Cell Selection Arm and Post-Transplant Cy Arm) are not allowed.	Minor modifications to the myeloablative regimens that involve start day or days of rest in the Control Arm are allowed but must be approved by the protocol chairs. Only minor modifications will be considered for approval. Modifications to the myeloablative regimens in the intervention arms (CD34 Cell Selection Arm and Post-Transplant Cy Arm) are not allowed. An additional day of rest may be added to conditioning regimens of any arm when transportation and/or delivery of the patient's graft is delayed.	Allow additional day of rest to conditioning regimens under certain unavoidable circumstances.
10.	Section 2.5.1. CD34 Selection Arm Page 2-11	Donors will be consented after recipients are randomized.	Unrelated donors will be consented after recipients are randomized.	Clarification

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11.	Section 2.5.1.2. Progenitor Cell Collection and Processing Page 2-14	*Not present in previous version.*	Cryopreservation: If it is determined after randomization that cryopreservation may be needed, it must be approved by the protocol chairs.	Addition of cryopreservation language
12.	Section 2.5.1.3. Bone Marrow Collection and Processing Page 2-14	*Not present in previous version*	Cryopreservation: If it is determined after randomization that cryopreservation may be needed, it must be approved by the protocol chairs.	Addition of cryopreservation language
13.	Section 2.6.1. Post-Transplant Cyclophosphamide Page 2-15	**Corticosteroids may not be used as an anti-emetic agent and should not be administered until 24 hours after the completion of post-transplantation cyclophosphamide, unless used for adrenal support or during a medical emergency (e.g. treatment of anaphylaxis).**	**Systemic corticosteroids may not be used as an anti-emetic agent and should not be administered until 24 hours after the completion of post-transplantation cyclophosphamide, unless clinically indicated.**	Clarified that ”systemic” steroids may used “if clinically indicated” prior to 24 hours after completion of post-transplant cyclophospha-mide

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14.	Section 3.2. Secondary Endpoints Page 3-3	*Not present in previous version*	3.2.7. Graft Failure Graft failure will be assessed as secondary endpoints, including primary graft failure and secondary graft failure. Primary graft failure is defined as no neutrophil recovery to $\geq$ 500 cells/µL by Day 28 post HSCT. Secondary graft failure will be assessed according to neutrophil count after initial hematologic recovery. Secondary graft failure is defined as initial neutrophil engraftment followed by subsequent decline in absolute neutrophil counts < 500 cells/µL for $\geq$ 3 days, unresponsive to growth factor therapy, but cannot be explained by disease relapse or medications. Assessment for this endpoint will occur up to two years post HSCT.	Addition of new secondary endpoint "graft failure"
15.	Section 4.4.1.1. Pre-Transplant Evaluations Page 4-5	• Infectious disease markers to include: CMV antibody, EBV antibody, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV-1 and -2, and HTLV-I and -II antibody, varicella zoster, and toxoplasmosis. (IgG and IgM) for	• Infectious disease markers to include: CMV antibody, EBV antibody, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV-1 and -2, and HTLV-I and -II antibody and varicella zoster. For patients randomized to the CD34 Cell	Clarification

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		patients randomized to the CD34 Cell Selection Arm. • CD34+ Selection arm only: Donor toxoplasmosis serologic evaluation (IgG and IgM). For both related and unrelated donors, toxoplasmosis testing will be performed at the transplant center. The transplant center must request additional 'day of collection' samples from the NMDP for unrelated donors in order to conduct the testing at their center.	Selection Arm, toxoplasmosis (IgG and IgM) must also be performed ≤ 56 days from the planned initiation of conditioning. • CD34+ Selection arm only: Donor toxoplasmosis serologic evaluation (IgG and IgM). For both related and unrelated donors, toxoplasmosis testing will be performed at the transplant center. The transplant center must request additional 'day of collection' samples from the NMDP for unrelated donors in order to conduct the testing at their center. Donor testing must be performed on or before day of transplant.	
16.	Section 4.4.1.1. Pre-Transplant Evaluations Page 4-5	Disease evaluation:…For MDS patients, Bone marrow aspirate must be performed ≤ 30 days prior to randomization and must be repeated if not within 6 weeks prior to the initiation of the transplant conditioning regimen.	Disease evaluation:…For MDS patients, Bone marrow aspirate must be performed ≤ 6 weeks prior to randomization and must be repeated if not within 6 weeks prior to the initiation of the transplant conditioning regimen.	Loosen requirements for MDS disease evaluation prior to conditioning
17.	Section 4.4.1.2. Post-Transplant Evaluations	CMV Monitoring: For patients on the CD34-selection arm, CMV monitoring through nucleic acid amplified testing	CMV Monitoring: For patients on the CD34-selection arm, CMV monitoring through nucleic acid amplified testing	Clarification

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	Page 4-6	(NAAT) will be done weekly through Day 100 and then at each clinical assessment until Day 180 post-transplant. For patients on the other 2 arms, CMV monitoring will be done according to institutional guidelines. It is *recommended* that weekly assessment for CMV be done through Day 63 post-transplant, and then at each clinical assessment until day 180 post-transplant.	(NAAT) will be done weekly through Day 100 and then at each clinical assessment until Day 180 post-transplant. For patients on the other 2 arms, CMV monitoring will be done according to institutional guidelines. It is *recommended* that weekly assessment for CMV be done through Day 63 post-transplant, and then at each clinical assessment until day 180 post-transplant. However, if both the recipient and the donor are CMV negative prior to transplant, CMV monitoring is not recommended unless clinically indicated.	
18.	Section 4.4.1.2. Post-Transplant Evaluations Page 4-7	CBC and WBC differential performed at least three times a week from Day 0 until ANC > 500/μL for 3 days and platelet count > 20,000/μL for 3 days (while hospitalized only) after nadir is reached. Thereafter, CBC weekly until Day 63 post-transplant, then every other week through Day 100 post-transplant, and then at Days 180, 270 and 365 post-transplant.	CBC and WBC differential performed at least three times a week from Day 0 until ANC > 500/μL for 3 days and platelet count > 20,000/μL for 3 days (while hospitalized only) after nadir is reached. Manual WBC differential is not required if WBC < 500/μL. Thereafter, CBC weekly until Day 63 post-transplant, then every other week through Day 100 post-transplant, and then at Days 180, 270 and 365 post-transplant.	Made manual WBC differential post-transplant requirements less restrictive.
19.	Section 4.4.6.2.1. Unanticipated	Section Header: "Unanticipated Adverse Device Effect Reporting"	Section Header: "Adverse Device Effect Reporting"	Clarification

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	Device Effect Reporting Page 4-11			
20.	Section 4.4.6.2.1. Adverse Device Effect Reporting Page 4-11	*Not present in previous version*	In addition, any SAE assessed by the investigators to be a direct result of the CliniMACS CD34 System requires reporting through an expedited AE reporting system within 24 hours of the investigator/clinical site becoming aware of the event.	New SAE reporting requirements
21.	Section 5.5.2. Analysis of Secondary Endpoints Page 5-5	*Not present in previous version*	5.5.2.7 Graft Failure Primary graft failure will be assessed as a secondary endpoint. The proportion of patients who do not achieve neutrophil recovery to $\geq$ 500 cells/μL by Day 28 post HSCT will be computed for each treatment arm and compared between the treatment arms using the Z test for binomial proportions.Secondary graft failure will be assessed as a secondary endpoint using cumulative incidence function. The cumulative incidence of secondary graft failure at 2 years post-	Addition of secondary endpoint graft failure

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			transplant will be computed along with 95% confidence intervals and compared between the treatment arms using Gray's test. Patients will be considered as reaching the endpoint if the initial neutrophil engraftment is followed by subsequent decline in absolute neutrophil counts < 500 cells/μL for ≥ 3 days, is unresponsive to growth factor therapy, and cannot be explained by disease relapse or medications. Death prior to secondary graft failure will be considered as a competing risk.	
22.	APPENDIX B-1 Patient Informed Consent Page B-11	"Risks and Toxicities Related to GVHD Prophylaxis"… .	"Risks and Toxicities Related to GVHD Prophylaxis"… If you were assigned to the CD34 Selection Arm and your cells are selected with the CliniMACS® CD34 Reagent System, you may receive low doses of iron, iron-dextran and monoclonal antibody when the selected cells are re-infused. Our experience shows that these low doses are unlikely to cause any bad side effects, including cancer.	Addition of new risk from Miltenyi CD34 Reagent IB, Version 8.0
23.	APPENDIX B-1 Patient Informed	**d. Lymphoproliferative Syndrome**: Patients in Treatment Group A (CD34	**d. Lymphoproliferative Syndrome:** Patients in Treatment Group A (CD34	Addition of new risk from

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	Consent Page B-13	Selected Peripheral Blood Stem Cell Graft) have an increased risk of developing post-transplant lymphoproliferative disorder (PTLD)…	Selected Peripheral Blood Stem Cell Graft) have an increased risk of developing post-transplant lymphoproliferative disorder (PTLD)… PTLD can be fatal.	Miltenyi CD34 Reagent IB, Version 8.0
24.	APPENDIX B-2 Related Donor Informed Consent Page B-32	7. T-Cell Depletion (CD34+ Selection)…	7. T-Cell Depletion (CD34+ Selection)… The CliniMACS CD34 Reagent System was approved by the FDA to treat patients with acute myeloid leukemia in first complete remission. It was approved on humanitarian grounds and its effectiveness has not been shown.	Addition of new information from Miltenyi CD34 Reagent IB, Version 8.0